Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Appendix: Azithromycin and the Risk of Cardiovascular Death

Table of Contents

This appendix provides supplementary material for the paper, including a more detailed presentation of several methodologic points. It should be read in conjunction with the primary paper.

METHODS

Inclusion-Exclusion Criteria

Serious illness exclusion. Patients with serious illnesses are excluded for two reasons. First, in such patients, antibiotic use may be a marker for a sudden decline that is difficult to measure. Second, out-of-hospital deaths related to the underlying illness may decrease the capacity to detect an acute medication effect. Consider, for example, sudden cardiac deaths, which will constitute a large proportion of out-of-hospital deaths. By definition, these must be "unexpected".[1] For terminal patients (e.g., patient with cancer metastases to the brain), deaths that occur outside of the hospital may not be unexpected. Sudden deaths in patients with substance abuse may be related to the drug (e.g., cocaine), and thus not meet the frequently employed definitions for sudden cardiac death.[1] Exclusion conditions are listed in Appendix Table 1.

Appendix Table 1. Exclusion conditions. **Unless otherwise indicated, codes are ICD9-CM diagnostic codes and a three/four digit code implies inclusion of all subcodes. Codes not listed are provided in the study protocol.**

Disease	Definition
1. Cancer	Diagnosis of cancer (except for non-melanomous skin cancers) or selected antineoplastic agents. Includes neoplasms uncertain behavior, ICD9-CM codes 235-238, except: 238.2 (skin), 238.9 (site unspecified), 237.70, 237.71 (neurofibromatosis), 238.4 (polycythemia v.), 238.7 (lymphoproliferative disease), 285.22 (anemia in neoplastic disease).
2. HIV	Diagnosis of HIV or use of antiretroviral agents appropriate for HIV or pentamadine (also used for other major immunocompromised patients)
3. Renal	Diagnosis or procedure code for dialysis outside of the hospital (includes 996.73). Also includes end-stage renal disease diagnosis (285.21, 585.5, 585.6), also outside of the hospital.
4. Liver	Diagnoses 570-573.
5. Respiratory	Diagnosis of respiratory failure, cardio-respiratory failure, or pulmonary heart disease. Also includes tracheostomy (excluding temporary), home oxygen, or home ventilator.
6. Organ transplant	Includes kidney, heart, lung, liver, bone marrow, and pancreas. Includes 996.8.
7. Serious neuromuscular	Multiple sclerosis (340), ALS (335.20), Duchenne's muscular dystrophy (335.21), Huntington's chorea (333.4), quadriplegia, paraplegia, or spinal cord injury. Recent stroke (inpatient with primary discharge diagnosis of 430, 431, 433.x1, 434, 436) with hemiplegia/hemiparesis (342, 438.2).
8. CV congenital anomalies (CA)	Common truncus (745.0) transposition great vessels (745.1), tetrology (745.2), common ventricle (745.3), endocardial cushion defect (745.6), pulmonary atresia (746.0), tricuspid atresia (746.1), hypoplastic left heart (746.7), coarctation of aorta (747.1), other anomalies of aorta (747.2), total anomalous pulmonary venous connection (747.41) . A single diagnosis is sufficient for exclusion.
9. Other CA/childhood conditions	Sickle cell (282.6), cerebral palsy (343), spina bifida (741), Down's syndrome (758.0), hydrocephalus (742.3), microcephalus (742.1), encephalocele (742.0), severe mental retardation (318.1, 318.2), cystic fibrosis.
10. Other end-stage illness	a. Hospice care. b. Diagnosis of coma, vegetative state , debility (799.3). c. Total parenteral nutrition, PEG, enteral feeding, malnutrition (260, 261,262, 263) when these are for outpatients. d. Gangrene (040, gas gangrene; 785.4 gangrene: single diagnosis sufficient) e. Intravenous medications outside of the hospital, as indicated by procedures for IV access outside a hospital stay period.
11. Drug abuse	Includes all medications and drugs with abuse potential and with the exception of alcohol (unless hospitalization with primary discharge diagnosis: 291.x, 303.x, 305.0, 980.0, 980.9, E860.0, E860.1, E860.9) and tobacco. Codes are 292.0 (drug withdrawal syndrome), 304.x (drug dependence), 305.2-305.9 (drug abuse, except alcohol/tobacco, 305.9 is abuse NOS, may be nonspecific, but better to exclude), 965.01 (accidental poisoning, heroin), 969.6 (poisoning, psychodysleptic [hallucinogens]), 970.81 (cocaine poisoning, added in 2010), E8500 (heroin poisoning), E8541 (psychodysleptic poisoning)

Inclusion-exclusion criteria. Study inclusion-exclusion criteria are listed in Appendix Table 2.

Appendix Table 2. Study prescription inclusion-exclusion criterion. **Applied as of t_0, the prescription fill date (or comparable date for nonuser controls).**

1. Known date of birth and gender;
2. Age 30-74 years at t_0. The lower age limit is present because sudden death in children and young adults is very rare (in our previous study, 27/1487 cases were for persons 15-29, who had 1/3 of cohort person-time [unpublished data]) and may have a different etiology.[2] The upper limit is present because in our experience the death certificate coded cause of death is less accurate for persons 75 and older;
3. Enrolled on t_0 in a category that provides full pharmacy benefits. Note for 2006 this definition must take into account the fact that persons with Medicare enrollment (those 65 years of age or older or those with qualifying disability) no longer have Medicaid pharmacy benefits because they obtain medications through Medicare part D;
4. Enrolled on the 365 days prior to t_0 (allowing gaps of <7 days), that is, the interval [t_0-365, t_0-1]. This assures sufficient enrollment to use medical encounters as measures of comorbidity.
5. At least one filled prescription in the 365 days preceding t_0. This assures that cohort members have some medical surveillance, which is important because baseline cardiovascular disease is defined from medical care encounters;
6. At least two encounters with a diagnosis in the period [t_0-365,t_0-1]. These include outpatient, ED, and inpatient encounters but do not include those for durable medical equipment. The encounters must meet the following additional criteria: they are separated by >30 days (for inpatient, date is admission date) and at least one falls in the period [t_0-183, t_0]. This further assures that cohort members are under ongoing medical surveillance, particularly near t_0.
7. Not residing in a nursing home or other residential institution on t_0 or at any time in the preceding 365 days, except for stays of <30 days following hospital discharge. Our previous experience suggests that for cardiovascular deaths, the coded cause of death on the death certificate is less accurate for nursing home residents. This includes inferred nursing home stays, defined as 2 or more outpatient encounters in the interval [t_0-365, t_0] with procedure indicating nursing home place of service separated by at least 28 days. It also includes external cause of injury diagnosis code indicating place of residence was an institution (E849.7).
8. No exclusion illness on t_0 or the preceding 365 days (Appendix Table 1).
9. On t_0 , not in the hospital (day of admission through discharge) or within 29 days of the discharge date. Events that occur in the hospital are not eligible for the study. The period shortly following hospital discharge is one of high risk and these events have a high prior likelihood of being related to the condition that led to hospitalization. We do not have information on medications given in the hospital and use of these could persist past discharge. Furthermore, medication use could change in the hospital and we would not know until the scheduled time for the next refill, or as long as 30 days following hospital discharge.
10. Only a single study antibiotic prescription* filled on t_0 (applied for antibiotic prescriptions only).

*Simultaneous fill for amoxicillin and amoxicillin+clavulanate potassium considered multiple fill.

Azithromycin Controls: Propensity Score Matching

We sought to identify four nonuser control periods for each of the 347,795 study azithromycin prescriptions. We required that the control periods have no current use of study antibiotics (azithromycin, amoxicillin, ciprofloxacin, levofloxacin) either on the day the period began (t_0) or in the preceding 29 days.

Because azithromycin users were likely to have a higher comorbidity burden than persons not receiving antibiotics, we matched the nonuser control periods according to azithromycin propensity score,[3] defined as the conditional probability of being an azithromycin user (versus nonuser), given the study covariates. We

considered using a standard algorithm for matching. However, this was not feasible, given that we would need to evaluate the propensity score, which included 153 covariates, for approximately 2 billion potential control periods (600,000 persons times 4,000+ days on which the period could begin). Thus, we utilized a more efficient sequential process to select the nonuser control periods.

A preliminary analysis with a random sample of approximately 1.6 million nonuser periods having distribution of age, sex, and calendar time comparable to that of azithromycin users identified four factors as important determinants of azithromycin use: more than 10 outpatient visits with a non-cardiovascular diagnosis in the past year, a prescription for a beta agonist in the past year, an emergency department visit in the past 30 days, or any filled prescription (other than azithromycin) in the past 30 days.

We used this information to identify a large pool of potential nonuser control periods from which we could then efficiently select the ultimate controls. The potential control pool consisted of 25 non-user periods for each azithromycin prescription, matched according to t_0, age, sex, and the four factors listed above. If 25 potential matching control periods could not be found for an individual azithromycin prescription, more potential controls were selected for subsequent prescriptions to achieve a mean of approximately 25 potential controls per azithromycin prescription. Ultimately, we identified a pool of 8,461,105 potential nonuser control periods.

Given this pool of potential control periods, we then calculated an azithromycin vs nonuser propensity score, using logistic regression. The propensity score was based upon 153 covariates; the odds ratios for the covariates are shown in Appendix Table 3.

The propensity score included a wide range of covariates. The range and number of covariates were necessary because of the broad study endpoint of cardiovascular mortality. The rationale for some key covariates is provided below.

1. Demographic factors included calendar month because both prescribing of antibiotics and mortality are affected by seasonal factors;
2. Respiratory and other factors related to antibiotic use were included because of the potential link between these factors (e.g., COPD) and mortality;
3. Given the focus on cardiovascular and sudden cardiac death, we included both cardiovascular medications and diagnoses in the propensity score. Although the contribution of any one variable may be small, inclusion of all of these variables provides a more comprehensive assessment of cardiovascular risk. We also sought to identify complications of diabetes, which are indicators of high-risk patients;
4. Psychiatric comorbidity is important because of the potential link to both cardiovascular and all-cause mortality, particularly given that the latter includes self-inflicted injuries;
5. Musculoskeletal conditions and injuries includes a detailed characterization of opioid use, important because poisoning/overdose deaths are a substantial fraction of non-cardiovascular deaths;
6. Neurologic comorbidity is potentially associated with elevated risk of deaths from a variety of causes;
7. Frailty indicators often characterize patients at high risk for death;
8. Medical care utilization is plausibly associated with mortality through at least two mechanisms. First, it can identify patients with particularly high acuity, for example, those with a recent hospital visit. Second, we have found that in the Tennessee Medicaid population persons without regular use of medical care have higher risk of cardiovascular death. The mechanism is likely to be related to failure to receive known beneficial interventions, such as beta-blockers in patients with serious coronary artery disease, or to behavioral factors, such as poor compliance.

Appendix Table 3. Azithromycin:nonuser control propensity score model. **25-1 sample.**

Obs	Parameter	DF	OR	CIlow	CIhigh	P ChiSq
1	Intercept	1	0.02466	0.02363	0.02573	<.0001
Demographic factors						
2	Race, white vs nonwhite	1	1.28497	1.27337	1.29667	<.0001
3	Female vs male	1	0.90542	0.89745	0.91347	<.0001
4	Age, 1 year increase	1	1.00192	1.00154	1.00229	<.0001
5	Standard Metropolitan Statistical Area (yes vs no)	1	0.95789	0.95109	0.96475	<.0001
6	Medicaid enrollment, disabled vs other	1	0.98397	0.9764	0.99161	<.0001
7	Calendar year 1992	1	0.9795	0.92322	1.03921	0.4926
8	Calendar year 1993	1	0.92582	0.88825	0.96499	0.0003
9	Calendar year 1994	1	0.84013	0.78127	0.90342	<.0001
10	Calendar year 1995	1	0.79734	0.71205	0.89284	<.0001
11	Calendar year 1996	1	0.82791	0.78477	0.87342	<.0001
12	Calendar year 1997	1	0.82992	0.79554	0.86579	<.0001
13	Calendar year 1998	1	0.81066	0.77714	0.84564	<.0001
14	Calendar year 1999	1	0.77591	0.74626	0.80674	<.0001
15	Calendar year 2000	1	0.80186	0.78022	0.8241	<.0001
16	Calendar year 2001	1	0.87645	0.86167	0.89148	<.0001
17	Calendar year 2002	1	0.9177	0.90345	0.93217	<.0001
18	Calendar year 2003	1	0.9718	0.95722	0.98661	0.0002
19	Calendar year 2004	1	0.94415	0.93019	0.95831	<.0001
20	Calendar year 2005	1	0.95248	0.93807	0.96711	<.0001
21	Calendar year 2006	0	1	1	1	.
22	January	1	0.92948	0.91596	0.94321	<.0001
23	February	1	0.96778	0.95376	0.982	<.0001
24	March	1	0.9138	0.90038	0.92741	<.0001
25	April	1	0.84815	0.83475	0.86178	<.0001
26	May	1	0.85571	0.84193	0.86972	<.0001
27	June	1	0.84724	0.83268	0.86205	<.0001
28	July	1	0.84851	0.83342	0.86389	<.0001
29	August	1	0.87806	0.863	0.89337	<.0001
30	September	1	0.90197	0.88759	0.91658	<.0001
31	October	1	0.91145	0.89751	0.92559	<.0001
32	November	1	0.93141	0.91772	0.9453	<.0001
33	December	0	1	1	1	.
Respiratory and other antibiotic-related						
34	Chronic obstructive pulmonary disease	1	0.86227	0.84879	0.87596	<.0001
35	Asthma	1	0.94958	0.93617	0.96318	<.0001
36	Respiratory disease hospitalization	1	0.89559	0.83477	0.96084	0.0021
37	Diagnosis indicating smoking	1	0.86946	0.85692	0.88218	<.0001
38	Nebulizer	1	1.06483	1.0376	1.09277	<.0001
39	Beta agonist	1	1.43785	1.4264	1.44939	<.0001
40	Other bronchodilator	1	1.11434	1.10119	1.12766	<.0001
41	Any antibiotic past 30 days	1	2.87405	2.84969	2.89862	<.0001

Cardiovascular, including diabetes						
42	Angina pectoris	1	1.03347	1.01411	1.05319	0.0006
43	Cardiac revascularization	1	1.03156	0.99234	1.07234	0.1162
44	Myocardial infarction	1	0.96056	0.91684	1.00637	0.0905
45	Other coronary heart disease	1	1.06579	1.05022	1.0816	<.0001
46	Cardiac valve disease	1	1.00883	0.98776	1.03034	0.4145
47	Conduction disorder	1	1.00941	0.96569	1.05511	0.6783
48	Atrial fibrillation	1	1.0369	1.00292	1.07202	0.033
49	Arrhythmia	1	1.00376	0.98544	1.02243	0.6894
50	Congestive heart failure	1	0.98846	0.9695	1.00779	0.2401
51	Stroke	1	0.93769	0.91046	0.96574	<.0001
52	Transient ischemic attack	1	1.04299	1.01134	1.07563	0.0074
53	Peripheral vascular disease	1	0.96601	0.94474	0.98776	0.0023
54	Obesity, diagnosed, not morbid	1	1.06637	1.0448	1.08838	<.0001
55	Morbid obesity, diagnosed	1	1.00949	0.98081	1.03901	0.5206
56	Hypertension	1	0.99359	0.9841	1.00317	0.1891
57	Malignant hypertension	1	0.98877	0.96603	1.01204	0.3412
58	Hyperlipidemia	1	1.00469	0.99454	1.01495	0.3661
59	Renal disease	1	0.93821	0.91081	0.96644	<.0001
60	Diabetes	1	0.99472	0.98117	1.00845	0.4491
61	Other cardiovascular disease	1	1.01507	1.00371	1.02656	0.0092
62	Cardiovascular symptoms past 30 days	1	2.35079	2.31904	2.38297	<.0001
63	New cardiovascular diagnosis, past 30 days	1	0.84981	0.83615	0.8637	<.0001
64	New cardiovascular medication, past 30 days	1	1.20809	1.18902	1.22746	<.0001
65	Diabetes, ocular complication	1	0.92798	0.9042	0.95238	<.0001
66	Diabetes, neurologic complication	1	1.00656	0.97898	1.03492	0.6444
67	Diabetes, skin complication	1	0.92639	0.89398	0.95998	<.0001
68	Diabetes, renal complication	1	0.92762	0.8781	0.97992	0.0073
69	Diabetes, other complication	1	1.01565	0.99392	1.03787	0.1594
70	Diabetes, poor control noted	1	0.9734	0.95726	0.9898	0.0016
71	Angiotensin-converting enzyme inhibitor	1	1.02446	1.01503	1.03398	<.0001
72	Angiotensin receptor blocker	1	1.08376	1.06986	1.09783	<.0001
73	Anticoagulant	1	0.98301	0.96266	1.00379	0.1084
74	Antiarrhythmic	1	1.05158	1.02067	1.08343	0.001
75	Aspirin	1	0.95045	0.93931	0.96172	<.0001
76	Beta-blocker	1	1.01526	1.0058	1.02481	0.0015
77	Calcium-channel blocker	1	1.01359	1.00389	1.0234	0.006
78	Digoxin	1	0.96488	0.94166	0.98867	0.004
79	Loop diuretic	1	1.04966	1.03862	1.06081	<.0001
80	Other diuretic	1	1.0135	1.00451	1.02257	0.0032
81	Insulin	1	1.01355	0.99613	1.03127	0.1281
82	Oral hypoglycemic	1	1.02437	1.00947	1.0395	0.0013
83	Statin	1	1.0059	0.99615	1.01575	0.2364
84	Fibrate lipid-lowering agent	1	1.00613	0.99061	1.02189	0.441
85	Nitrate anti-anginal	1	0.98135	0.96767	0.99523	0.0086
86	Other antihypertensive	1	0.9664	0.95197	0.98104	<.0001
87	Peripheral vasodilator	1	1.06681	1.03219	1.10259	0.0001
88	Platelet inhibitor, not aspirin	1	0.98225	0.96418	1.00065	0.0586

Psychiatric						
89	Schizophrenia	1	0.78309	0.76747	0.79903	<.0001
90	Alcohol abuse	1	0.76319	0.7431	0.78382	<.0001
91	Psychiatric hospitalization	1	1.02092	1.0029	1.03925	0.0227
92	Cyclic antidepressant	1	0.96779	0.9584	0.97727	<.0001
93	SSRI/SNRI antidepressant	1	1.08004	1.0715	1.08864	<.0001
94	Trazodone	1	0.97143	0.9601	0.98288	<.0001
95	Other antidepressant	1	1.02573	1.01488	1.0367	<.0001
96	Benzodiazepine/GABA agonist	1	1.21402	1.20445	1.22367	<.0001
97	Antipsychotic	1	0.83571	0.82533	0.84622	<.0001
98	Lithium	1	0.88624	0.85864	0.91473	<.0001
99	Mood stabilizer	1	1.01977	1.00911	1.03054	0.0003
100	Hydroxyzine	1	1.06951	1.05892	1.08021	<.0001
Musculoskeletal and injury-related						
101	Inflammatory arthropathy	1	1.05667	1.03932	1.0743	<.0001
102	Opioid poisoning	1	0.92706	0.86283	0.99606	0.0387
103	Psychotropic poisoning	1	0.95351	0.90545	1.00413	0.0713
104	Poisoning, unspecified medication	1	1.12219	1.08506	1.16059	<.0001
105	Suicide attempt	1	0.88791	0.84623	0.93164	<.0001
106	Fall	1	0.97538	0.96082	0.99017	0.0012
107	Injury ED, 1-2 visits	1	0.95417	0.94332	0.96514	<.0001
108	Injury ED, 3+ visits	1	0.93152	0.90939	0.95419	<.0001
109	Injury outpatient, 1-2 visits	1	1.03338	1.02407	1.04277	<.0001
110	Injury outpatient, 3-5 visits	1	1.02015	1.00326	1.03732	0.0192
111	Injury outpatient, 6+ visits	1	0.96453	0.93762	0.9922	0.0123
112	Morphine Rx past 12 months	1	0.88525	0.86861	0.90221	<.0001
113	Fentanyl Rx past 12 months	1	0.94324	0.92748	0.95927	<.0001
114	Meperidine Rx past 12 months	1	1.05624	1.03838	1.07441	<.0001
115	Opioids past 30 days, 1-15 days	1	0.87111	0.86132	0.881	<.0001
116	Opioids past 30 days, 16-30 days	1	1.00571	0.99095	1.02068	0.4505
117	Opioids past 30 days, 31+ days	1	0.97706	0.9599	0.99453	0.0103
118	Opioids past year, 1-60 days	1	1.14436	1.1306	1.15829	<.0001
119	Opioids past year, 61-499 days	1	1.14479	1.12544	1.16447	<.0001
120	Opioids past year, 500+ days	1	1.1576	1.12422	1.19197	<.0001
121	Opioid refill, early	1	1.08083	1.0611	1.10093	<.0001
122	Disease modifying anti-rheumatic drug	1	0.95196	0.92998	0.97446	<.0001
123	Systemic corticosteroid	1	1.12743	1.10398	1.15138	<.0001
Neurologic						
124	Seizure disorder	1	0.89905	0.87925	0.9193	<.0001
125	Dementia	1	0.91069	0.88036	0.94205	<.0001
126	Anticonvulsant	1	0.99935	0.98071	1.01835	0.9464
127	Parkinsons medication	1	0.91569	0.89485	0.93702	<.0001
Frailty						
128	Decubitus ulcer	1	0.93937	0.88265	0.99973	0.049
129	Amputation	1	0.90509	0.82272	0.99571	0.0405
130	Delirium	1	0.8697	0.82851	0.91293	<.0001
131	Incontinence, urine	1	1.01858	0.99701	1.04062	0.0918
132	Incontinence, fecal	1	0.99218	0.91288	1.07838	0.8535
133	Indwelling urinary catheter	1	0.92295	0.84696	1.00576	0.0674
134	Feeding/nutrition problem	1	0.90354	0.83487	0.97786	0.0119
135	Wheelchair or walker	1	0.97218	0.94924	0.99568	0.0206
Medical care						
136	Any outpatient visit past 30 days	1	0.94775	0.93968	0.9559	<.0001
137	Any prescription past 30 days (not study antibiotic)	1	0.62543	0.61764	0.63332	<.0001
138	CV inpatient visit 91-365 days before t0	1	1.02644	1.00662	1.04665	0.0087
139	CV inpatient visit 30-90 days before t0	1	0.84372	0.81744	0.87085	<.0001
140	CV days hospital stay 5+	1	0.89348	0.8668	0.92099	<.0001

141	Non-CV hospitalization	1	0.9195	0.90924	0.92987	<.0001
142	Cardiovascular ED visit	1	1.02416	1.01341	1.03503	<.0001
143	Non-CV ED visit	1	1.04723	1.03787	1.05667	<.0001
144	Non-CV ED visit past 30 days	1	1.04147	1.02587	1.05731	<.0001
145	CV ED visit past 30 days	1	0.78475	0.76565	0.80432	<.0001
146	Any ED visit past 7 days	1	2.84565	2.7928	2.89951	<.0001
147	CV outpat visits past year: 1	1	1.03304	1.02136	1.04485	<.0001
148	CV outpat visits past year: 2-5	1	1.02579	1.01428	1.03743	<.0001
149	CV outpat visits past year: 6-10	1	1.02795	1.01191	1.04424	0.0006
150	CV outpat visits past year: >10	1	1.04764	1.02549	1.07027	<.0001
151	Non-CV outpat visits past year: 1	1	1.16631	1.11935	1.21523	<.0001
152	Non-CV outpat visits past year: 2-5	1	1.35895	1.31181	1.40778	<.0001
153	Non-CV outpat visits past year: 6-10	1	1.62298	1.56662	1.68138	<.0001
154	Non-CV outpat visits past year: >10	1	1.50944	1.45669	1.56411	<.0001
155	Scale	0	2.71828	2.71828	2.71828	_

Important percentiles for the azithromycin:nonuser control propensity score are shown in Appendix Table 4.

Appendix Table 4. Azithromycin:nonuser control propensity score percentiles.

	Potential nonuser control	Azithromycin
	Propensity Score	
Minimum	0.0031	0.0041
5%	0.0161	0.0200
25%	0.0234	0.0292
50%	0.0303	0.0420
75%	0.0420	0.0774
95%	0.0918	0.1738
Maximum	0.6530	0.6227

For each azithromycin prescription, four nonuser control periods were selected from the potential control pool, frequency-matched according to propensity score. The first step was to create propensity score bands: we identified 100 1-percentile intervals, each with an approximately equal number of azithromycin prescriptions. From each of these bands, 4n control periods were randomly selected, where n was the number of azithromycin prescriptions within the band. For this reason, the nonuser control periods are not individually matched on either the propensity score or any of the study variables. Because the very highest band (99th percentile) did not contain sufficient controls, the successive lower bands were oversampled to make up the deficiency.

A key test of propensity score matching is whether or not the distribution of the covariates is balanced. The manuscript Table 1 shows virtually complete balance with regard to study covariates.

Study Followup and Person-Time

The unit of study analysis is the *course of antibiotic therapy*, a fixed period of time beginning with the antibiotic prescription. Because azithromycin nearly always is prescribed for a 5-day course and the other study antibiotics most commonly have a 10 day course, the analysis considered both 5 and 10 day periods. In addition, we also separately analyzed days 6-10, which for azithromycin corresponded to recent, but not current use. The analysis nearly always included the full 5 or 10 day periods, but these were censored if either the study eligibility criteria ceased to be met or there was a subsequent prescription for a study antibiotic.

The followup for control periods was 10 days. Followup for the control periods ended for the same reasons as for the study antibiotics; followup also ended if a study antibiotic prescription was filled.

Endpoints

Cardiovascular deaths were identified from the computerized death certificate file. These had an underlying cause of death consistent with a cardiovascular cause (ICD-9 codes 390-459, 798.1, 798.2, 798.9, 799.9 and comparable ICD10 codes).

Sudden cardiac death[4-6] was defined as a sudden pulseless condition that was fatal, consistent with a ventricular tachyarrhythmia, and occurred in the absence of a known noncardiac condition as the proximate cause of the death.[5] This excluded deaths of patients admitted to the hospital, that were not sudden, or with evidence for an extrinsic (e.g., cocaine) or noncardiac (e.g., pneumonia) etiology or a different cardiac etiology (e.g., heart failure).

Sudden cardiac deaths were identified from a previously developed and validated computerized definition that utilized multiple sources of data, including computerized death certificates, hospital discharge files, and Medicaid files with terminal outpatient medical care encounters.[1] It identified qualifying deaths that occurred outside of the hospital or other institution, had an underlying cause of death compatible with sudden cardiac death, and no evidence of care on the day of death inconsistent with a sudden cardiac death. The definition, designed to be specific, was developed from 926 out-of-hospital deaths adjudicated by medical record review. It utilized multiple sources of data, including computerized death certificates, hospital discharge files, and other terminal outpatient medical care encounters (Appendix). The positive predictive value of the definition was 86% in the development study, with an estimated sensitivity of 75%. In an independent validation study, this definition had a positive predictive value of 88%.[1]

Antibiotic Indication

The Medicaid records of filled prescriptions do not include information on drug indication. Thus, we assigned a presumptive indication from medical care encounters during the period t_0 and the preceding 29 days.

First, we developed a list of detailed diagnoses that were possible indications for the study antibiotics. We then recorded the occurrence of a primary or secondary diagnosis corresponding to one of these conditions in an emergency department or other physician encounter. We also recorded whether the encounter occurred in the more recent period--t_0 and the preceding 6 days--or more remotely.

The indication was then assigned giving priority to diagnoses that were more recent. Within the more recent diagnoses, priority was given to emergency department visits and to primary diagnoses. When there were multiple diagnoses of equal priority, we assigned highest priority to diagnoses of more serious illnesses: pneumonia, COPD, pyrexia unknown origin, cardiac infections, brain/spinal infections, and other serious bacterial infections. If we failed to assign an indication within the recent period, a diagnosis was sought during the more remote period, following the above procedure.

For approximately one-third of prescriptions, no indication was assigned. There are two common scenarios in which this occurs. The first is prescription of the antibiotic during a visit for another health condition: for example, a patient with a visit related to arthritis also complains of symptoms consistent with sinusitis. In this circumstance, the diagnosis leading to the antibiotic prescription may not be recorded. The second is prescribing by phone, which is common for antibiotics but which does not result in a reimbursed medical care encounter and thus there will not be a diagnosis in our database.

Statistical Analysis

The unit of analysis for the study was the course of antibiotic therapy, consisting of either 5- or 10-day periods beginning with t_0. The analysis estimated the cumulative incidence of death during these periods. Because the periods were occasionally censored, the analysis used proportional hazards regression.

For this study, the underlying population is that of Tennessee Medicaid enrollees who have either a study antibiotic prescription or who have some portion of their Medicaid experience selected as a nonuser control period. Each person will appear in the analysis for only those time intervals: either a prescription or a control period. All study covariates (primarily reflected in the propensity score) are updated at the beginning of the time interval. Thus, these data satisfy independence assumptions: the time intervals are nonoverlapping and only 1 event can occur for each person.[7] We performed an alternative analysis that explicitly considered possible within-person dependencies with essentially identical findings (Appendix Table 10).

The baseline covariates in the regression models were age, sex, calendar year, and estimated propensity score, expressed as deciles. Given the 10-day maximum length of study followup, there were no time-dependent covariates.

Several of the analyses utilized a summary score for baseline cardiovascular disease risk which combined the large number of baseline comorbidity variables. The *cardiovascular disease risk score* was defined as the probability of cardiovascular death as a function of these baseline covariates, conditional on no study antibiotic exposure.[8] The probabilities were estimated from a Poisson regression model (for efficiency, given large number covariates) with the baseline covariates and study antibiotic type and then expressed as 20 quantiles. There was more than a 50-fold difference in the rate of cardiovascular death between the highest and lowest quantiles of the risk score.

The cardiovascular disease risk score was used in two ways in the analysis. For the description of the cohort groups at baseline, it provided a single summary measure of how baseline cardiovascular risk varied according to antibiotic use status. For this purpose, the disease risk score was considered a continuous variable, taking on values from 0 (lowest quantile) to 19 (highest quantile).

In the planned analysis of how antibiotic effects varied according to baseline cardiovascular risk, deciles of the cardiovascular disease risk score were used to define the appropriate subgroups. These were calculated by combining adjoining quantiles of the score.

Propensity Score Distributions: Amoxicillin/Ciprofloxacin/Levofloxacin Analyses

Given that a primary study hypothesis involved the comparison between azithromycin use and use of no antibiotic, the nonuser control periods were matched to the propensity score distribution of azithromycin users. There also was an antibiotic control group that included qualifying prescriptions for amoxicillin. Furthermore, ciprofloxacin and levofloxacin were included in the cohort to quantify their cardiovascular safety relative to azithromycin. Use of these control groups involved six comparisons: 1) amoxicillin versus nonuser controls; 2) azithromycin vs amoxicillin; 3) ciprofloxacin vs amoxicillin; 4) levofloxacin vs amoxicillin; 5) azithromycin versus ciprofloxacin; and 6) azithromycin versus levofloxacin. To adjust for potential comorbidity differences, we calculated a separate propensity score for each, using the same covariates as for the azithromycin:control propensity score, except that the antibiotic:antibiotic propensity scores also included antibiotic indication. Important quantiles for those propensity scores are shown in Appendix Table 5.

Appendix Table 5. Percentiles for other study antibiotic propensity scores.

		N	Min	P5	P25	P50	P75	P95	Max
Amoxicillin vs nonuser	Amoxicillin								
	No	1391180	0.042579	0.149002	0.222731	0.289014	0.372291	0.763472	0.993369
	Yes	1348672	0.04879	0.207406	0.358349	0.822118	0.927004	0.978623	0.99553
Azithromycin vs amoxicillin	Azithromycin								
	No	1348672	0.000664	0.005074	0.018192	0.052255	0.295193	0.484113	0.866628
	Yes	347795	0.001145	0.068093	0.292857	0.386622	0.49003	0.649625	0.872965
Ciprofloxacin vs amoxicillin	Ciprofloxacin								
	No	1348672	0.002086	0.008307	0.022776	0.073864	0.177116	0.36137	0.984417
	Yes	264626	0.003003	0.05582	0.175478	0.294214	0.650018	0.843497	0.982692
Levofloxacin vs amoxicillin	Levofloxacin								
	No	1348672	0.000028	0.000112	0.000459	0.022239	0.135482	0.380596	0.950497
	Yes	193906	0.000086	0.072816	0.194758	0.326647	0.509395	0.76376	0.981095
Azithromycin vs ciprofloxacin	Azithromycin								
	No	264626	0.000341	0.021692	0.098407	0.332648	0.637896	0.839545	0.965997
	Yes	347795	0.001172	0.328532	0.63447	0.762775	0.850359	0.91212	0.969241
Azithromycin vs levofloxacin	Azithromycin								
	No	193906	0.020447	0.154103	0.411815	0.586152	0.697891	0.811713	0.996074
	Yes	347795	0.031599	0.408812	0.616686	0.71601	0.798385	0.929049	0.997775

One important check of the specification of the propensity score model is whether or not, after adjustment for propensity score, the distribution of the covariates is balanced. We performed this check for the azithromycin:amoxicillin propensity score using a variant of the inverse probability of treatment method[9] described by Brenner *et al*.[10] The advantage of this method is that it standardizes the distribution of the amoxicillin group to that of the azithromycin group, which is left unadjusted. The method of Brenner *et al* works as follows: for patient i, let r_i be the variable value in the group providing the standard and s_i that in the group being standardized. Then the weight is defined as r_i/s_i. Thus, for the amoxicillin:azithromycin propensity scores, considering the ith patient in the amoxicillin group, r_i is the probability of treatment with azithromycin, given a comparable covariate pattern. This is simply the propensity score for that patient. Similarly, s_i is the probability of treatment with amoxicillin, which is 1-propensity score.

Appendix Table 6 shows excellent covariate balance after standardizing the covariate distributions for the amoxicillin group.

Appendix Table 6. Propensity-score adjusted characteristics of antibiotic prescriptions and nonuser control periods[a].

	Nonuser	Amoxicillin[b]	Azithromycin
N of prescriptions	1,391,180	1,348,672	347,795
Demographic characteristics			
Calendar year t_0, mean	2003.1	2003.1	2003.1
Age in years, mean	48.6	48.7	48.6
Female, %	77.5%	77.5%	77.5%
White, %	79.7%	79.2%	79.1%
Urban residence,%	50.3%	51.0%	50.8%
Medicaid enrollment disability,%	49.5%	49.9%	49.6%
Cardiovascular medications, %			
Angiotensin converting enzyme inhibitors	28.1%	28.2%	28.1%
Anti-arrhythmic	1.6%	1.6%	1.6%
Anticoagulants	3.5%	3.5%	3.5%
Non-aspirin platelet inhibitor	5.0%	5.0%	4.9%
Beta-blockers	21.6%	21.7%	21.5%
Calcium-channel blockers	20.2%	20.4%	20.2%
Digoxin	2.5%	2.6%	2.5%
Loop diuretic	17.3%	17.5%	17.2%
Other diuretic	25.9%	26.1%	25.9%
Nitrate	10.2%	10.2%	10.1%
Statin	28.1%	28.3%	28.0%
Cardiovascular diagnoses, %			
Myocardial infarction	0.7%	0.7%	0.7%
Revascularization	1.2%	1.2%	1.2%
Cardiac valve disease	3.0%	3.0%	3.0%
Heart failure	4.3%	4.4%	4.3%
Cerebrovascular disease	2.6%	2.6%	2.6%
Peripheral vascular disease	2.9%	2.9%	2.9%
Cardiovascular risk summary			
Summary cardiovascular risk score, mean[c]	9.2	9.3	9.3
Other comorbidity, %			
Insulin	6.5%	6.5%	6.5%
Oral hypoglycemic	16.5%	16.6%	16.5%
Antipsychotic prescription	11.5%	11.8%	11.8%
Beta agonist	40.5%	40.6%	40.3%
Chronic obstructive pulmonary disease	5.5%	5.4%	5.4%
Asthma	7.1%	7.2%	7.1%
Corticosteroid	3.3%	3.4%	3.3%
Any prior antibiotic past 30 days	27.9%	27.7%	27.0%
Frailty indicators, %			
Complications of diabetes[d]	7.4%	7.3%	7.5%
Incontinence of urine or feces	2.9%	2.9%	2.9%
Indwelling urinary catheter	0.2%	0.2%	0.2%
Decubitus ulcer	0.3%	0.3%	0.3%
Wheelchair or walker	2.3%	2.3%	2.3%
Medical care utilization, %			
Hospitalization, cardiovascular	7.2%	7.2%	7.2%
Hospitalization, other	15.7%	15.8%	15.8%
Emergency department , cardiovascular	20.7%	20.8%	20.7%
Emergency department, other	52.0%	51.8%	51.9%
Emergency department, past 30 days	13.9%	14.1%	13.9%

[a]For 365 days preceding t_0 unless otherwise specified. [b]Includes amoxicillin with potassium clavulanate. [c]Score based on 20 quantiles: from 0 (lowest risk 5% of cohort) to 19 (highest risk 5%). [d]Includes dermatologic, neurologic, ocular and renal complications as well as hypoglycemia, hyperglycemia, diabetic coma, diabetic ketoacidosis, and other complications.

RESULTS

Cohort Characteristics

Appendix Table 7 shows the cohort characteristics at the time of filling of study antibiotic prescriptions and beginning of nonuser control periods.

Appendix Table 7. Cohort characteristics at t_0. t_0 is the time of filling of study antibiotic prescriptions and beginning of nonuser control periods.[a]

	Nonuser	Amoxicillin[b]	Ciprofloxacin	Levofloxacin	Azithromycin
N of prescriptions	1,391,180	1,348,672	264,626	193,906	347,795
Demographic characteristics					
Calendar year t_0, mean	2003.1	1999.6[§]	2001.3[§]	2003.4[§]	2003.1
Age in years, mean	48.6	47.7[§]	50.5[§]	51.5[§]	48.6
Female, %	77.5%	73.3%[§]	75.5%[§]	73.5%[§]	77.5%
White, %	79.7%	74.6%[§]	74.8%[§]	78.4%[§]	79.1%[§]
Urban residence,%	50.3%	51.6%[§]	50.3%	49.1%[§]	50.8%[§]
Medicaid enrollment disability,%	49.5%	50.6%[§]	56.7%[§]	56.8%[§]	49.6%
Cardiovascular medications, %					
Angiotensin converting enzyme inhibitors	28.1%	24.0%[§]	28.4%[§]	32.8%[§]	28.1%
Anti-arrhythmic	1.6%	1.3%[§]	1.8%[§]	2.4%[§]	1.6%
Anticoagulants	3.5%	3.3%[§]	4.2%[§]	5.4%[§]	3.5%
Non-aspirin platelet inhibitor	5.0%	2.9%[§]	5.3%[§]	7.4%[§]	4.9%
Beta-blockers	21.6%	17.3%[§]	20.9%[§]	24.8%[§]	21.5%
Calcium-channel blockers	20.2%	19.9%[§]	22.8%[§]	24.3%[§]	20.2%
Digoxin	2.5%	3.5%[§]	3.8%[§]	3.6%[§]	2.5%
Loop diuretic	17.3%	15.1%[§]	20.1%[§]	23.8%[§]	17.2%
Other diuretic	25.9%	22.4%[§]	26.3%[§]	28.9%[§]	25.9%
Nitrate	10.2%	9.6%[§]	11.4%[§]	13.3%[§]	10.1%
Statin	28.1%	17.9%[§]	25.2%[§]	34.5%[§]	28.0%
Cardiovascular diagnoses, %					
Myocardial infarction	0.7%	0.7%	0.8%[§]	0.8%[§]	0.7%
Revascularization	1.2%	1.0%[§]	1.2%	1.6%[§]	1.2%
Cardiac valve disease	3.0%	2.9%[§]	3.1%	3.8%[§]	3.0%
Heart failure	4.3%	3.9%[§]	5.3%[§]	6.8%[§]	4.3%
Cerebrovascular disease	2.6%	2.3%[§]	3.3%[§]	3.7%[§]	2.6%
Peripheral vascular disease	2.9%	2.4%[§]	3.8%[§]	4.9%[§]	2.9%
Cardiovascular risk summary					
Summary cardiovascular risk score, mean[c]	9.2	9.5[§]	10.3[§]	10.6[§]	9.3
Other comorbidity, %					
Insulin	6.5%	6.9%[§]	10.2%[§]	10.2%[§]	6.5%
Oral hypoglycemic	16.5%	13.1%[§]	18.9%[§]	21.9%[§]	16.5%
Antipsychotic prescription	11.5%	8.8%[§]	11.3%[§]	13.3%[§]	11.8%[§]
Beta agonist	40.5%	28.1%[§]	28.6%[§]	43.5%[§]	40.3%
Chronic obstructive pulmonary disease	5.5%	4.6%[§]	5.1%[§]	6.8%[§]	5.4%
Asthma	7.1%	4.8%[§]	5.1%[§]	7.4%[§]	7.1%
Corticosteroid	3.3%	2.8%[§]	3.8%[§]	4.8%[§]	3.3%
Any prior antibiotic past 30 days	27.9%	28.4%[§]	38.6%[§]	40.3%[§]	27.0%[§]
Frailty indicators, %					
Complications of diabetes[d]	7.4%	6.5%[§]	11.3%[§]	11.7%[§]	7.5%
Incontinence of urine or feces	2.9%	2.1%[§]	4.6%[§]	4.3%[§]	2.9%
Indwelling urinary catheter	0.2%	0.2%	0.5%[§]	0.4%[§]	0.2%
Decubitus ulcer	0.3%	0.4%[§]	1.1%[§]	0.9%[§]	0.3%
Wheelchair or walker	2.3%	1.6%[§]	3.2%[§]	3.8%[§]	2.3%
Medical care utilization, %					
Hospitalization, cardiovascular	7.2%	6.0%[§]	8.5%[§]	9.5%[§]	7.2%
Hospitalization, other	15.7%	14.8%[§]	19.1%[§]	20.4%[§]	15.8%
Emergency department , cardiovascular	20.7%	15.7%[§]	19.0%[§]	23.3%[§]	20.7%
Emergency department, other	52.0%	46.6%[§]	50.7%[§]	54.0%[§]	51.9%
Emergency department, past 30 days	13.9%	11.3%[§]	15.6%[§]	18.0%[§]	13.9%

[a]For 365 days preceding t_0 unless otherwise specified. [b]Includes amoxicillin with potassium clavulanate. [c]Score based on 20 quantiles: from 0 (lowest risk 5% of cohort) to 19 (highest risk 5%). [d]Includes dermatologic, neurologic, ocular and renal complications as well as hypoglycemia, hyperglycemia, diabetic coma, diabetic ketoacidosis, and other complications.

[§] indicates $p<.01$ for comparison with nonuser controls.

Appendix Table 8 shows the recorded indications for the study antibiotics as well as the days of prescribed therapy.

Appendix Table 8. Study antibiotic indications. **Also includes days of prescribed therapy.**

	Amoxicillin	Ciprofloxacin	Levofloxacin	Azithromycin
Days of prescribed therapy				
Median	10	10	10	5
Inter-quartile range	8-10	7-10	7-10	5-5
Recorded indication, % [a]				
Ear-nose-throat	50.7	16.3	24.4	41.8
Bronchitis	12.3	5.7	13.3	19.9
Pneumonia	1.1	1.1	4.5	2.3
Respiratory symptoms	6.7	5.4	10.3	12.6
Chronic obstructive pulmonary disease	4.4	4.2	9.1	6.9
Other respiratory	2.9	1.4	2.3	3.2
Gastrointestinal	1.5	3.2	1.5	0.8
Genitourinary	5.3	44.8	18.7	3.4
Skin/soft tissue/joint/bone	5.4	9.1	7.4	2.5
Wounds	5.1	5.6	4.8	3.4
Pyrexia unknown origin	0.7	0.9	1.3	1.1
Other serious infections [b]	1.1	1.1	1.0	0.8
Other	3.0	1.3	1.4	1.5

[a]Based on proportion with known indication. Indication not recorded for 30.1%, 36.0%, 31.2, and 24.7% of azithromycin, amoxicillin, ciprofloxacin, and levofloxacin prescriptions, respectively.
[b]Includes blood infections, cardiac infections, central nervous system infections, and other systemic bacterial infections.

As a further test of the performance of the azithromycin:amoxicillin propensity score, we assessed balance in recorded indication after inverse probability of treatment weighting (Appendix Table 9), using the same method as for Appendix Table 6 (see above).

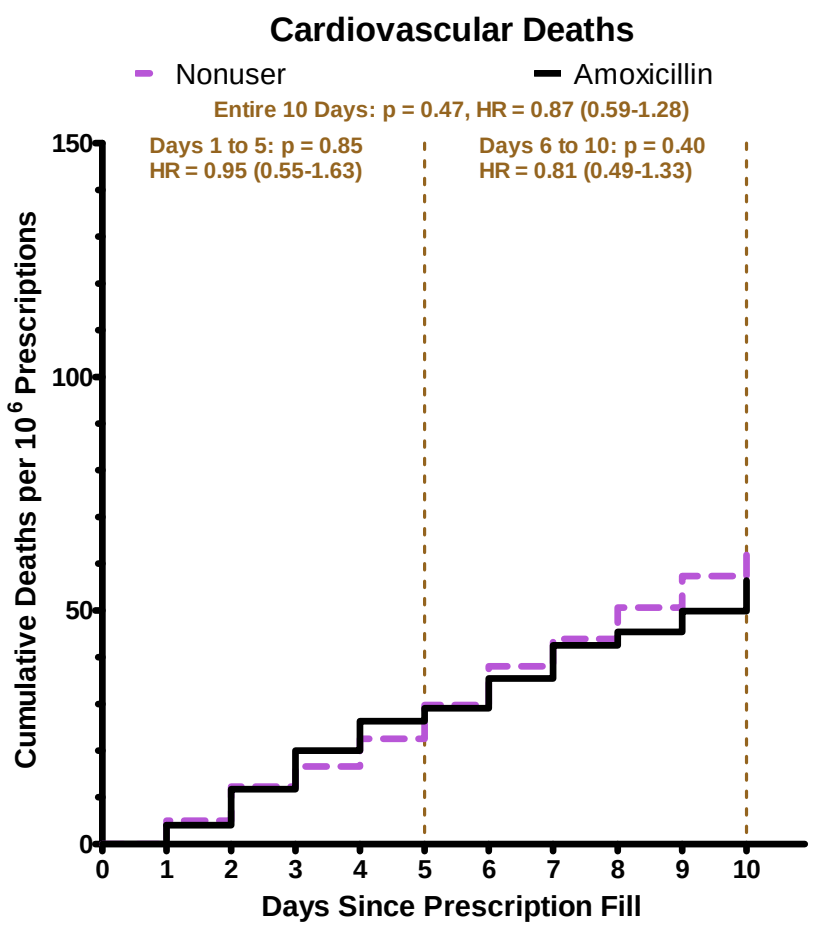
Appendix Table 9. Propensity-score adjusted antibiotic indications[a].

	Amoxicillin	Azithromycin
Days of prescribed therapy		
Median	10	5
Inter-quartile range	8-10	5-5
Recorded indication, % [a]		
Ear-nose-throat	41.8	41.8
Bronchitis	19.7	20.0
Pneumonia	2.5	2.4
Respiratory symptoms	12.6	12.6
Chronic obstructive pulmonary disease	6.8	6.9
Other respiratory	3.2	3.2
Gastrointestinal	0.8	0.8
Genitourinary	3.5	3.4
Skin/soft tissue/joint/bone	2.5	2.4
Wounds	3.3	3.4
Pyrexia unknown origin	1.1	1.1
Other serious infections[b]	0.8	0.7
Other	1.5	1.5

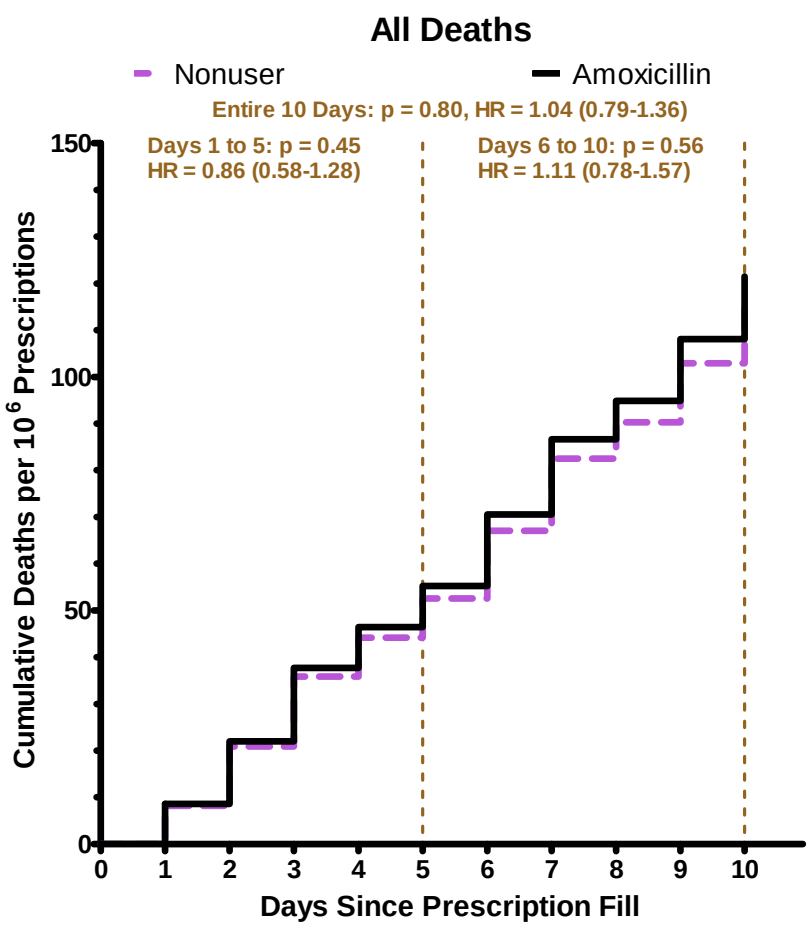
[a]Based on proportion with known indication, see MS Table 2. The propensity score is for azithromycin vs amoxicillin.
[b]Includes blood infections, cardiac infections, central nervous system infections, and other systemic bacterial infections.

Cardiovascular and Total Mortality

Appendix Figure 1 shows cardiovascular and total mortality for amoxicillin users versus nonuser controls.



Deaths:										
Amoxicillin	6	11	12	9	4	9	10	4	6	9
Nonuser	7	10	6	8	10	11	8	9	9	6



Deaths:										
Amoxicillin	11	17	20	11	11	19	20	10	16	16
Nonuser	17	15	19	12	16	19	14	15	19	13

Appendix Figure 1. Cardiovascular and total mortality for amoxicillin users versus nonuser controls. ***See also MS Figure 1.***

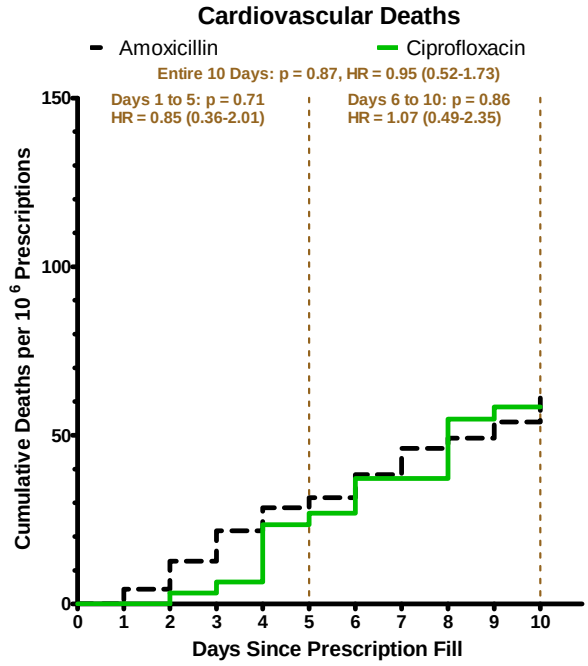
Appendix Table 10 shows the full results from the regression model for the primary analysis of azithromycin 5 day course of therapy versus comparable period for amoxicillin, for the cardiovascular death endpoint.

The regression model coefficients for the study covariates must be interpreted cautiously. Because controlling for confounding relies upon the propensity score, these coefficients are not completely adjusted for other factors. For example, male sex is associated with increased risk. However, the corresponding HRs for these covariates are not well adjusted for other cardiovascular risk factors, as the propensity score can only be demonstrated to perform this adjustment for azithromycin.

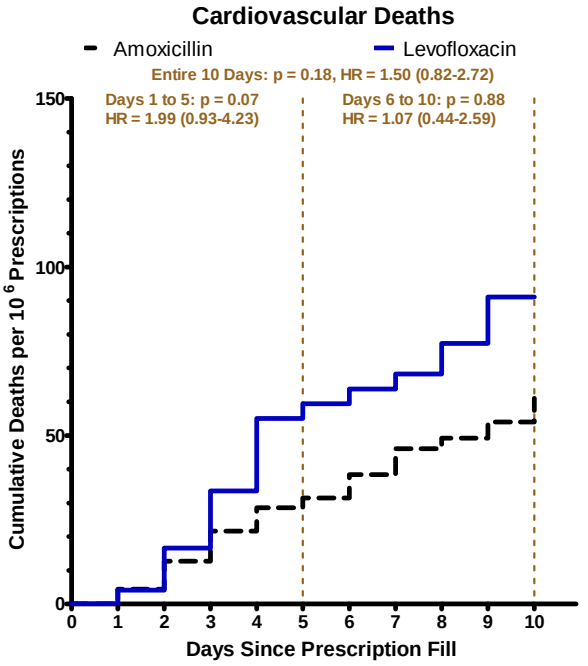
Appendix Table 10. Proportional hazards regression model estimates. **These are for azithromycin 5 day course of therapy versus comparable period for amoxicillin, cardiovascular death endpoint.**

Obs	Parameter	ClassVal0	Prob ChiSq	Hazard Ratio	CL Low	CL High
1	Year before 1995		0.4179	1.5253	0.5490	4.2360
2	Age, 1 year increase		<.0001	1.0551	1.0330	1.0770
3	Female vs male		<.0001	0.3461	0.2150	0.5560
4	Antibiotic	4: azithromycin	0.0025	2.4909	1.3790	4.5010
5	Propensity Score Decile	9	0.0675	4.7179	0.8940	24.8870
6		8	0.2658	2.6600	0.4750	14.9000
7		7	0.1557	3.3763	0.6290	18.1160
8		6	0.7043	0.6687	0.0840	5.3420
9		5	0.9109	1.1149	0.1660	7.4960
10		4	0.2334	2.4878	0.5560	11.1390
11		3	0.1396	2.7965	0.7150	10.9420
12		2	0.1358	2.7582	0.7270	10.4600
13		1	0.4808	1.6736	0.4000	7.0050

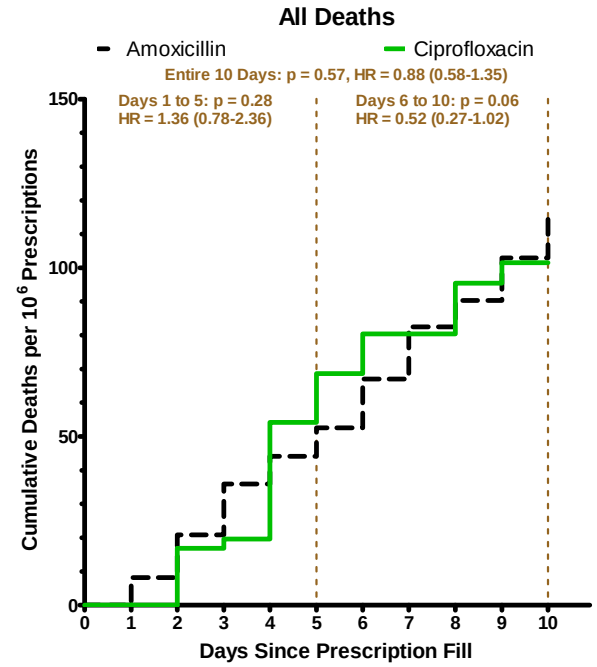
Appendix Figure 2 shows cardiovascular and total mortality for the comparison of ciprofloxacin and levofloxacin versus amoxicillin.



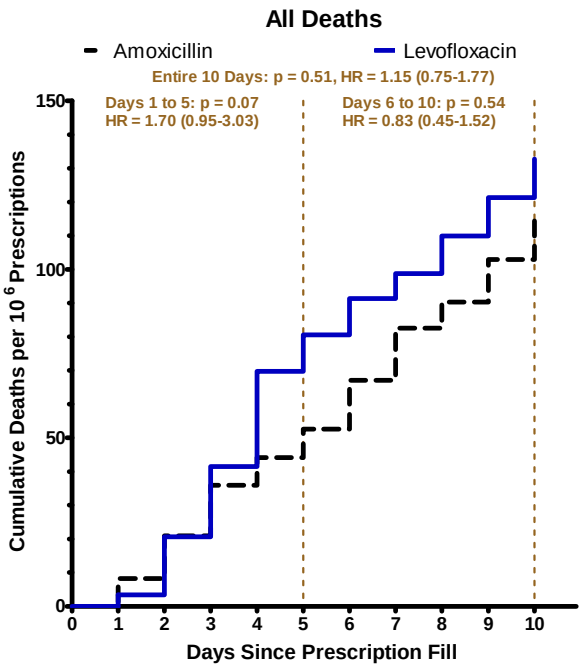
Deaths:										
Ciprofloxacin	0	1	1	5	1	3	0	5	1	0
Amoxicillin	6	11	12	9	4	9	10	4	6	9



Deaths:										
Levofloxacin	1	3	4	5	1	1	1	2	3	0
Amoxicillin	6	11	12	9	4	9	10	4	6	9



Deaths:										
Ciprofloxacin	0	6	1	12	5	4	0	5	2	0
Amoxicillin	11	17	20	11	11	19	20	10	16	16



Deaths:										
Levofloxacin	1	5	6	8	3	3	2	3	3	3
Amoxicillin	11	17	20	11	11	19	20	10	16	16

Appendix Figure 2. Cardiovascular and total mortality for the comparison of ciprofloxacin and levofloxacin versus amoxicillin. See also MS Figure 2.

Appendix Table 11 shows alternative analyses for the comparison of cardiovascular deaths during a 5 day course of azithromycin therapy versus a comparable time period for amoxicillin. The analyses include a propensity-score stratified analysis, in which we calculated the HR for each decile of the azithromycin: amoxicillin propensity score. The model for each stratum included age and gender. The pooled estimated was calculated as the inverse-variance weighted mean of the stratum-specific estimates.[11] The pooled HR was 2.53 (1.37-4.67), essentially identical to that of 2.49 (1.38-4.50) from the primary analysis. We also performed the same analysis for the azithromycin vs nonuser control comparison; the HR from the propensity-score stratified analysis was 3.01 (1.84-4.94), very similar to that of 2.88 (1.79-4.63) from the primary analysis.

We also performed a repeated measures analysis that controls for possible within-person dependencies (although theoretically the use of non-overlapping time periods and only one endpoint per person should make this unnecessary) as well as one that includes terms for other potentially proarrhythmic drugs. The latter include non-study macrolides/fluoroquinolones, methadone,[12] anti-arrhythmic medications that can cause torsade de pointes (disopyramide, procainamide, amiodarone, sotalol, quinidine, dofetilide),[13;14] cisapride,[15] terfenadine,[16] and astemizole.[17] Findings for both of these analyses were essentially identical to those of the primary analysis.

Appendix Table 11. Alternative analyses.

	All Cardiovascular Death HR	*95% CI*
Primary analysis	2.49	1.38-4.50
Propensity-score stratified analysis	2.53	1.37-4.67
Repeated measures analysis to control for possible dependence between different time periods within the same patient.	2.49	1.40-4.42
Model includes terms for other proarrhythmic drugs	2.51	1.38-4.54

For azithromycin users, the absolute excess risk of cardiovascular disease increased markedly with increasing cardiovascular disease risk score (MS Figure 3). Appendix Table 12 shows how several of the individual components of the cardiovascular disease risk score varied according to score deciles. The data are for azithromycin users, with characteristics ascertained as of the date of the prescription fill.

Appendix Table 12. Azithromycin user characteristics according to cardiovascular risk score deciles.
Characteristics are those as of the date of the prescription fill. Also see footnotes to MS Table 1.

	Deciles 1-5	**Deciles 6-9**	**Decile 10**
N of prescriptions	179,317	135,931	32,547
Demographic characteristics			
Calendar year t_0, mean	2003.2	2002.9	2002.7
Age in years, mean	42.7	53.9	59.4
Female, %	91.7%	66.8%	43.7%
White, %	81.6%	76.8%	74.8%
Urban residence,%	48.8%	52.4%	55.4%
Medicaid enrollment disability,%	33.0%	64.5%	79.3%
Cardiovascular medications, %			
Angiotensin converting enzyme inhibitors	16.8%	36.6%	54.9%
Anti-arrhythmic	0.9%	1.7%	4.5%
Anticoagulants	1.6%	4.0%	12.4%
Non-aspirin platelet inhibitor	2.3%	6.3%	13.7%
Beta-blockers	13.4%	26.9%	44.0%
Calcium-channel blockers	11.7%	26.9%	38.6%
Digoxin	0.2%	2.0%	17.9%
Loop diuretic	7.3%	22.4%	50.0%
Other diuretic	19.5%	31.8%	36.7%
Nitrate	4.1%	12.9%	31.1%
Statin	19.0%	35.4%	46.8%
Cardiovascular diagnoses, %			
Myocardial infarction	0.1%	0.8%	3.1%
Revascularization	0.9%	1.4%	2.1%
Cardiac valve disease	1.8%	3.4%	7.6%
Heart failure	0.5%	4.0%	27.0%
Cerebrovascular disease	1.9%	2.7%	5.9%
Peripheral vascular disease	1.1%	3.6%	9.3%
Cardiovascular risk summary			
Summary cardiovascular risk score, mean	4.4	13.4	18.5
Other comorbidity, %			
Insulin	3.5%	7.8%	17.1%
Oral hypoglycemic	11.6%	20.2%	28.4%
Antipsychotic prescription	6.1%	16.3%	24.8%
Beta agonist	35.5%	44.0%	51.4%
Chronic obstructive pulmonary disease	3.0%	7.2%	11.3%
Asthma	7.5%	7.0%	5.7%
Corticosteroid	1.8%	4.4%	7.0%
Any prior antibiotic past 30 days	26.4%	27.2%	29.1%
Frailty indicators, %			
Complications of diabetes	5.2%	8.7%	14.8%
Incontinence of urine or feces	2.6%	3.1%	3.6%
Indwelling urinary catheter	0.3%	0.0%	0.0%
Decubitus ulcer	0.1%	0.3%	1.7%
Wheelchair or walker	1.3%	2.8%	5.8%
Medical care utilization, %			
Hospitalization, cardiovascular	4.2%	8.1%	19.9%
Hospitalization, other	15.8%	14.6%	20.3%
Emergency department , cardiovascular	18.5%	21.0%	31.4%
Emergency department, other	54.8%	48.0%	51.9%
Emergency department, past 30 days	11.8%	14.7%	22.0%

Reference List

(1) Chung CP, Murray KT, Stein CM, Hall K, Ray WA. A computer case definition for sudden cardiac death. *Pharmacoepidemiol Drug Saf* 2010;19:563-572.

(2) Liberthson RR. Sudden death from cardiac causes in children and young adults. *N Engl J Med* 1996;334:1039-1044.

(3) Glynn RJ, Schneeweiss S, Sturmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol* 2006;98:253-259.

(4) Marcus FI, Cobb LA, Edwards JE et al. Mechanism of death and prevalence of myocardial ischemic symptoms in the terminal event after acute myocardial infarction. *Am J Cardiol* 1988;61:8-15.

(5) Siscovick DS, Raghunathan TE, Psaty BM et al. Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med* 1994;330:1852-1857.

(6) Albert CM, Hennekens CH, O'Donnell CJ et al. Fish consumption and risk of sudden cardiac death. *JAMA* 1998;279:23-28.

(7) Arnold SF. Mathematical statistics. *Prentice-Hall* 1990;157.

(8) Arbogast PG, Kaltenbach L, Ding H, Ray WA. Adjustment of multiple cardiovascular risk factors with a summary risk score. *Epidemiol* 2008;19:30-37.

(9) Sturmer T, Schneeweiss S, Brookhart MA, Rothman KJ, Avorn J, Glynn RJ. Analytic strategies to adjust confounding using exposure propensity scores and disease risk scores: Nonsteroidal antiinflammatory drugs and short-term mortality in the elderly. *Am J Epi* 2005;161:891-898.

(10) Brenner H, Arndt V, Gefeller O, Hakulinen T. An alternative approach to age adjustment of cancer survival rates. *Eur J Cancer* 2004;40:2317-2322.

(11) Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. *Methods for meta-analysis in medical research.* New York, NY: John Wiley and Sons, 2000.

(12) Pearson EC, Woosley RL. QT prolongation and torsades de pointes among methadone users: reports to the FDA spontaneous reporting system. *Pharmacol Drug Safety* 2005;14:747-753.

(13) Murray KT, Roden DM. Disorders of cardiac repolarization: The long QT syndromes. In: Crawford MH, DiMarco JO, Paulus WJ, eds. *Cardiology*. 2nd ed. Mosby; 2004;765-774.

(14) Damkier P, Hansen LL, Brosen K. Effect of diclofoenac, disulfiram, itraconazole, grapefruit juice and erythromycin on the pharmacokinetics of quinidine. *Br J Clin Pharmacol* 1999;48:829-838.

(15) Wiseman LR, Faulds D. Cisapride. An updated review of its pharmacology and therapeutic efficacy as a prokinetic agent in gastrointestinal motility disorders. *Drugs* 1994;47:116-152.

(16) Monahan BP, Ferguson CL, Killeavy ES, Lloyd B.K., Troy J, Cantilena LR. Torsades de pointes occurring in association with terfenadine use. *JAMA* 1990;264:2788-2790.

(17) Matsumoto S, Yamazoe Y. Involvement of multiple human cytochromes P450 in the liver microsomal metabollism of astemizole and a comparison with terfenadine. *Br J Clin Pharmacol* 2001;51:133-142.